Toxicology Reports 8 (2021) 1394–1398

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Sinus bradycardia is associated with poor outcome in critically ill patients with COVID-19 due to the B.1.1.7 Lineage

Athanasios Chalkias [a,b,*,1], Ioannis Pantazopoulos [c,1], Nikolaos Papagiannakis [d], Anargyros Skoulakis [a], Eleni Laou [a], Konstantina Kolonia [a], Nicoletta Ntalarizou [a], Konstantinos Tourlakopoulos [e], Athanasios Pagonis [e], Christos Kampolis [f], Luis García De Guadiana Romualdo [g], Dimitrios Ragias [a], Jesper Eugen-Olsen [h], Konstantinos Gourgoulianis [e], Eleni Arnaoutoglou [a], for the SPARCOL Investigators

[a] University of Thessaly, School of Health Sciences, Faculty of Medicine, Department of Anesthesiology, Larisa, Greece
[b] Outcomes Research Consortium, Cleveland, OH, 44195, USA
[c] University of Thessaly, School of Health Sciences, Faculty of Medicine, Department of Emergency Medicine, Larisa, Greece
[d] National and Kapodistrian University of Athens, Medical School, Eginition University Hospital, First Department of Neurology, Athens, Greece
[e] University of Thessaly, School of Health Sciences, Faculty of Medicine, Department of Respiratory Medicine, Larisa, Greece
[f] Hippokrateion University Hospital, Department of Emergency Medicine, Athens, Greece
[g] Hospital Universitario Santa Lucía, Laboratory Medicine Department, Cartagena, Spain
[h] Copenhagen University Hospital Hvidovre, Department of Clinical Research, Hvidovre, Denmark

ARTICLE INFO

Handling Editor: Dr. Aristidis Tsatsakis

Keywords:
COVID-19
B.1.1.7 variant
Bradycardia
Intensive care unit
Outcome

ABSTRACT

The progress of COVID-19 from moderate to severe may be precipitous, while the characteristics of the disease are heterogenous. The aim of this study was to describe the development of sinus bradycardia in critically ill patients with COVID-19 and its association with outcome in outbreak due to the SARS-CoV-2 B.1.1.7 Lineage. We leveraged the multi-center SuPAR in Adult Patients With COVID-19 (SPARCOL) study and identified patients who required admission to intensive care unit (ICU). Inclusion criteria were: (a) adult (≥18 years old) patients hospitalized primarily for COVID-19; (b) a confirmed SARS-CoV-2 infection diagnosed through reverse transcriptase polymerase chain reaction test of nasopharyngeal or oropharyngeal samples; and (c) at least one blood sample collected at admission and stored for suPAR, hs-CRP, and ferritin testing. All patients had continuous heart rate monitoring during hospitalization. In total, 81 patients were included. Of them, 17 (21 %) and 64 (79 %) were intubated and admitted to the ICU during the first and second wave, respectively. Two (12 %) and 62 (97 %) developed bradycardia before ICU admission, respectively ($p < 0.001$). Patients with bradycardia had increased suPAR ($p < 0.001$) and hs-CRP level ($p < 0.001$). Infusion of isoprenaline and/or noradrenaline was necessary to maintain an adequate rate and peripheral perfusion in all patients. Mortality was significantly higher in patients with bradycardia ($p < 0.001$). In conclusion, bradycardia was associated with poor outcome. As B.1.1.7 variant strain is spreading more rapidly in many countries, our findings help in the identification of patients who may require early admission to ICU.

1. Introduction

Coronavirus outbreaks are a global public health threat due to their high capacity for mutation and recombination [1]. Although several months have been passed after the inception of the SARS-CoV-2 pandemic, the numbers of critically ill patients with severe coronavirus disease 2019 (COVID-19) are increasing in many European countries.

COVID-19 is a lower respiratory tract infection, but arrhythmias and other cardiovascular symptoms are frequently reported. Cardiac arrhythmias may contribute to morbidity and mortality and have been observed in up to 44.4 % of COVID-19 patients, depending on the

* Corresponding author at: University Hospital of Larisa, Department of Anesthesiology, 41110 Biopolis, Mezourlo, Larisa, Greece.
E-mail address: thanoschalkias@yahoo.gr (A. Chalkias).
[1] These authors equally contributed to the study.

https://doi.org/10.1016/j.toxrep.2021.07.004
Received 19 May 2021; Received in revised form 21 June 2021; Accepted 7 July 2021
Available online 8 July 2021

severity of the disease [2,3]. In a recent study of 113 COVID-19 patients requiring intensive care unit (ICU) treatment, 50 episodes of sustained atrial tachycardias, 5 episodes of sustained ventricular arrhythmias, and 30 bradycardic events were documented [4]. Only 5 bradycardic events were associated with hemodynamic deterioration; however, whether bradycardia is associated with worse outcomes remains unknown.

A new variant of SARS-CoV-2 was first detected in the United Kingdom in September 2020. This variant, called B.1.1.7, is known to spread more easily and may be more deadly than previous variants. To date, the new variant has spread to more than 90 countries worldwide, and further diagnostic measures are needed to prevent additional mortality [5]. In a recent genetic analysis in Greece, the B.1.1.7/UK linage (Variant VOC_202012) was reported in 88.4 % of the samples, while in a previous analysis the same variant was reported in only 1.3 % of the samples [6]. On the contrary, the main variants during the first wave (March - July 2020) were the B.1.1, B.1, and B.1.1.74. Since December 2020, the British variant has become widespread also in Spain, constituting around 15–20 % of the cases [7]. The aim of this study was to describe the development of sinus bradycardia in critically ill patients with COVID-19 and its association with outcome in outbreak due to the SARS-CoV-2 B.1.1.7 Lineage.

2. Materials and methods

2.1. The SuPAR in adult patients with COVID-19 study

We leveraged the SuPAR in Adult Patients With COVID-19 (SPARCOL) study (ClinicalTrials.gov Identifier: NCT04590794) and included consecutive patients requiring ICU admission. The primary aim of the study was to estimate the incidence of sinus bradycardia (sustained sinus rhythm with a resting heart rate ≤60 bmp, diagnosed and monitored with continuous heart rate monitoring) and its clinical implications in patients with COVID-19.

The Institutional Review Board of the University Hospital of Larisa approved the study (IRB no. 17543). The study was performed according to national and international guidelines and consent procedures were obtained. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines for observational cohort studies [8].

2.2. Study design and outcomes definitions

We collected data from 252 COVID-19 patients during the period of April 1st to December 31st, 2020, the date the database was locked for the purpose of this analysis. Also, we divided the study period into two consecutive cohorts according to the duration of the two COVID-19 waves in most European countries (April 2020 - July 2020 and August 2020 - December 2020).

In order to decrease the effects of comorbidities and the associated medication on cardiac rhythm and rate, we excluded from this analysis patients with confirmed SARS-CoV-2 infection who were not primarily admitted for COVID-19, patients with incomplete data, patients with pre-existing severe cardiac or respiratory disease, such as heart failure, more than mild chronic obstructive pulmonary disease or pulmonary vascular disease, patients with pacemaker/implantable cardioverter-defibrillator, and patients who were intubated due to cardiac arrest.

2.3. Statistical analysis

Statistical analysis was performed using R v4.0. Differences between numerical observations in the first and second wave were detected using the non-parametric Mann-Whitney test. The chi-square test of independence was applied to the categorical observations, while in both cases, the Benjamini-Hochberg false discovery rate correction was applied to account for the multiple number of tests. In this study, adjusted p-values less than 0.05 were deemed significant. For linear correlation we used Spearman's rho coefficient. A logistic regression model was fitted with the presence of bradycardia as the dependent factor and wave and the different probable confounding factors as independent variables. A log-likelihood test was used to assess the significance of each term. The respective odds ratio and p-value was computed for each variable, while no adjustment was applied in the resulting p-values from this model.

3. Results

In total, 252 consecutive patients were hospitalized for COVID-19 and 81 (32 %) required intubation and ICU admission [first wave 17 (21 %); second wave 64 (79 %)]. Of them, two (12 %) and 62 (97 %) patients from the first and second wave, respectively, developed sinus bradycardia before ICU admission (Table 1, Fig. 1). In the second wave, the average time for development of bradycardia was 5 and 10 days from admission and onset of symptoms, respectively.

All patients developed bradycardia without clinically detectable myocardial necrosis and none of them was receiving drugs inducing bradycardia, such as hydroxychloroquine, moxifloxacin, azithromycin, or remdesivir. There were no statistically significant differences in comorbidities or prior medication between patients with and without bradycardia. In all patients with bradycardia, infusion of isoprenaline and/or noradrenaline was necessary to maintain an adequate rate and peripheral perfusion before intubation and especially during ICU stay. In both waves, the dose of isoprenaline and norepinephrine increased during ICU stay, with patients of the second wave requiring higher infusion rates ($p < 0.001$) (Fig. 2).

Mortality was higher in patients with bradycardia (64 % vs. 11 %, p

Table 1
Clinical and laboratory characteristics at ICU admission and outcome (N = 81).

		Without bradycardia	With bradycardia	Adjusted p-value
Age (years), mean (SD)		66.2 (12.6)	69.1 (10.8)	0.071
Wave	First, n (%)	15 (19)	2 (2)	<0.001
	Second, n (%)	2 (2)	62 (77)	
Sex - Male, n (%)		9 (11)	44 (54)	0.019
Smoking - Yes, n (%)		7 (9)	18 (22)	0.05
APACHE II, mean (SD)		10.86 (4.7)	17.36 (4)	<0.001
SOFA, mean (SD)		10.73 (2.5)	12.63 (2.2)	<0.001
Heart rate (beats per minute), mean (SD)	No b-blocker	73.3 (6.75)	55.2 (6.73)	<0.001
	Prior use of b-blocker*	–	51.3 (6.13)	–
Mean arterial pressure (mmHg), mean (SD)		87.28 (10.1)	81.28 (12.1)	<0.001
PaO_2/FiO_2 ratio, mean (SD)		204.24 (78.4)	128.75 (56.9)	<0.001
pH, mean (SD)		7.36 (0.1)	7.28 (0.1)	<0.001
Temperature (°C), mean (SD)		37.91 (0.8)	38.44 (1)	<0.001
Hemoglobin (g/dL), mean (SD)		10.97 (1.9)	11.39 (9.1)	0.297
White blood cells (K/uL), mean (SD)		9.52 (4.9)	10.29 (5.2)	0.118
High-sensitivity CRP (mg/L), mean (SD)		3.2 (4.7)	13.27 (23.1)	<0.001
D-Dimers (ng/mL), mean (SD)		1020.53 (1259.9)	1369.94 (1238.4)	<0.001
Ferritin (ng/mL), mean (SD)		3970.3 (1253.8)	2628.32 (4363.8)	0.011
suPAR (ng/mL), mean (SD)#		7.65 (5.2)	9.07 (4.3)	<0.001
Lactate (mmol/L), mean (SD)		2.09 (1.5)	4.96 (3.6)	<0.001
Outcome	Death, n (%)	9 (11)	52 (64)	<0.001
	Hospital discharge, n (%)	10 (12)	10 (12)	

ICU, intensive care unit; CRP, C-reactive protein.

* Six patients of the second wave were on chronic antihypertensive treatment with b-blockers (bisoprolol, n = 2; nebivolol, n = 4), but all of them received the last dose more than 48 h before admission.

Measured at hospital admission.

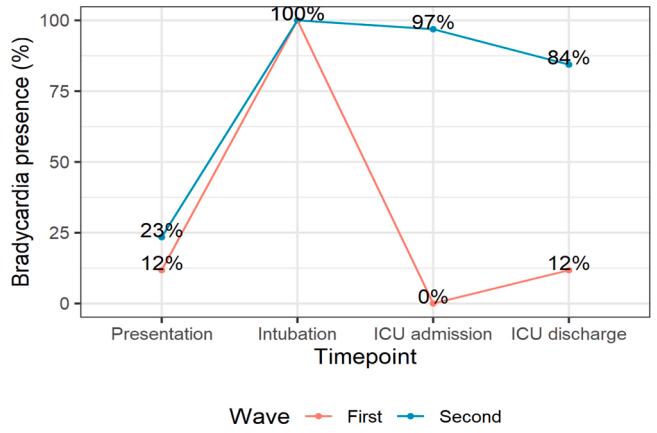

Fig. 1. Clinical course of patients who developed bradycardia during hospitalization (first wave, n = 2; second wave, n = 62). All of them had bradycardia by the time of intubation. ICU, intensive care unit.

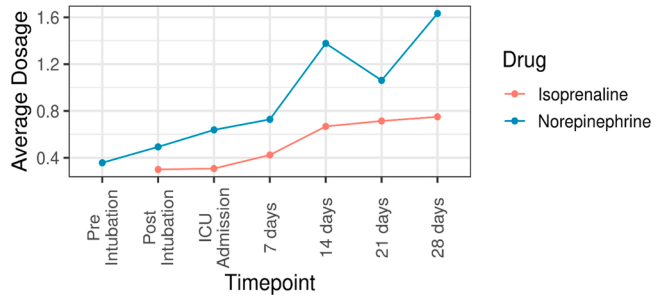

Fig. 2. Average dose of isoprenaline and noradrenaline in our patients (n = 81). The dose of isoprenaline was significantly higher during the second wave (p = 0.026) in contrast to this of norepinephrine (p = 0.051).
ICU, Intensive Care Unit.

< 0.001). After adjusting for different confounding factors (age, sex) and different comorbidities, such as COPD, diabetes mellitus, kidney injury, respiratory or other types of infection, preexisting arrhythmia, or cardiovascular comorbidities, only the onset of bradycardia was associated with mortality (p < 0.001). All survivors had bradycardia at ICU discharge.

4. Discussion

The most important finding in this study was the association between the development of bradycardia and poor outcome. In our patients, bradycardia developed without clinically detectable myocardial necrosis, while none of them was receiving drugs inducing bradycardia. Until now, patient characteristics, baseline electrocardiogram features, respiratory function, serum biomarkers of inflammation, and myocardial injury had an insufficient discriminatory power to identify subjects at increased risk for the development of new electrocardiogram changes [9]. Although rhythm disorders have been described in several case series, our cohort is the largest with sinus bradycardia so far. Our results suggest an inhibitory influence of the B.1.1.7 variant on cardiac conduction system and considering the high mortality worldwide, we recommend close monitoring of patients with COVID-19 due to the SARS-CoV-2 B.1.1.7 Lineage.

In a recent UK cohort study including patients hospitalized from November 9 to December 20, 2020, B.1.1.7 was associated with an increased viral load but not with severe disease [10]. However, other studies have suggested an association between viral load and mortality [11]. The B.1.1.7 variant may have been introduced and transmitted in European countries long before the first relevant announcement in early December, 2020. Patients infected with the B.1.1.7 variant seem to be younger, with fewer comorbidities, but with an increased risk of hospitalization per case associated with B.1.1.7 on a population level [12]. In our patients, the average time for development of bradycardia was significantly shorter compared to other cohorts, but similar to the UK cohort [9,10].

The underlying pathophysiology and pathogenesis of bradycardia is complex and several mechanisms may be implicated in its development. In our cohort, suPAR and hs-CRP were significantly higher in patients with bradycardia. suPAR level ≥ 6 ng/mL has been independently associated with the development of organ failure in patients with COVID-19 [13–15], and therefore, bradycardia may be associated with the severity of inflammation and disease progression. In addition, proinflammatory cytokines released upon pulmonary infection activate vagal afferent and subsequent vagal efferent signaling [16]. The latter are a main component of the cholinergic anti-inflammatory pathway that modulates the inflammatory response through interaction with peripheral α7 subunit-containing nicotinic acetylcholine receptors (nAChRs) [17]. Animal studies have shown that it is possible to activate the cholinergic anti-inflammatory pathway by delivering an electrical charge that is below the threshold required to significantly change heart rate because the neural tracts descending in the vagus nerve to modulate immune responses function at a lower firing threshold than the cardio-inhibitory fibers [18,19]. Therefore, the initial activation of the cholinergic anti-inflammatory pathway may not affect chronotropy, but excessive pathway activity may increase heart rate because the activation of α7 nAchRs elicits a sympathetic cardiovascular response [20,21]. Moreover, SARS-CoV-2-induced neuronal cell death pauperizes angiotensin-converting enzyme 2 receptors in the cardiovascular loci of central nervous system leading to prolonged activation of the sympathetic system with concomitant reduced vagal activity [22]. When vagus nerve activity is deficient, inflammation is excessive [19], which may explain the higher ferritin levels in the non-bradycardic group.

The lower (but still higher than normal) ferritin levels in the bradycardic patients, together with the increased levels of suPAR and hs-CRP, may reflect a more severe disease and a heightened activity of the cholinergic anti-inflammatory pathway. However, the onset of bradycardia in our patients may imply an increased and amplified binding of SARS-CoV-2 Spike glycoproteins to the α7nAChRs, which prevents the immunosuppressive effects of acetylcholine and decreases heart rate [23,24], as well increased vagal activity. In addition, the absence of myocardial necrosis together with the increase in D-Dimer may indicate other uncharacterized pathways of electrical conduction defects. An increase in blood pressure in patients with COVID-19, caused by the severe inflammatory response and/or in an effort to maintain tissue oxygenation, may lead to turbulent microcirculatory blood flow. The resulting higher or lower (than physiological) shear stress impairs endothelial homeostasis, with the affected endothelium displaying a hypercoagulant/prothrombotic/pro-oxidant state that hinders microvascular reactivity [25]. The impaired microcirculatory blood flow, together with the increased levels of inflammatory mediators, enhance the mechanical stress of cardiomyocytes and metabolic demands of conduction muscle cells, promoting metabolic instability and conduction disorders [26]. Moreover, SARS-CoV-2 genes may also encode K^{+} channels and dysregulate the action potential and Ca2+ handing in cardiomyocytes, while excessive inflammation can further modulate the function of several ion channels, leading to QT prolongation and arrhythmias [1,15]. Further research is necessary for the elucidation of the underlying mechanisms of bradycardia in patients with COVID-19.

Based on our experience, the use of drugs that increase proinflammatory cytokine production or those affecting the conduction system of the heart should be avoided in patients with the B.1.1.7 variant, especially in those with established sinus bradycardia or other conduction disorders [27–31]. Moreover, the use of anticholinergics, such as atropine, could inhibit the protective effects of the cholinergic anti-inflammatory pathway. In these patients, transcutaneous or

transvenous pacing may be ineffective or unavailable and isoprenaline should be the first line medication for the treatment of bradycardia, especially before endotracheal intubation [30]. Moreover, isoprenaline induces vasodilation through β2 adrenoceptor stimulation in arteriolar smooth muscle and may improve microvascular blood flow and tissue oxygenation [32].

The study has several strengths. It is a multicenter study that relied on collection of clinical, laboratory, and outcome data throughout the COVID-19 hospitalization during two successive outbreak waves, capturing a diverse patient population. Data collection was systematic and all patients admitted/intubated during the period April 1st to December 31st 2020 were enrolled. Our sample was limited to patients consecutively hospitalized specifically for COVID-19 and without receiving any specific treatment besides dexamethasone, allowing for a better description of the effects of SARS-CoV-2 infection on different organs of the human body. The major limitations of the present study are the relatively small sample and its observational nature. Despite the careful analysis, it is not possible to fully account for all potential confounders and therefore, the study cannot be trusted *per se* as a basis of clinical decision. However, our findings have significant implications for a better understanding of the pathophysiology of COVID-19 and for better planning and organization in the future.

5. Conclusions

Development of bradycardia during hospitalization was associated with poor outcome. As B.1.1.7 variant strain is spreading more rapidly in many countries, our findings are important and can help in the classification of novel COVID-19 phenotypes for identifying populations that may benefit from early admission to ICU.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

Athanasios Chalkias: conceptualization, methodology, resources, supervision, data curation, visualization, writing- original draft preparation, writing-review and editing

Ioannis Pantazopoulos: conceptualization, methodology, resources, supervision, data curation, visualization, writing- original draft preparation, writing-review and editing

Nikolaos Papagiannakis: Formal analysis, resources, data curation, visualization, writing-review and editing

Anargyros Skoulakis: resources, data curation, visualization, writing-review and editing

Eleni Laou: methodology, resources, data curation, visualization, writing-review and editing

Konstantina Kolonia: resources, data curation, visualization, writing-review and editing

Nicoletta Ntalarizou: resources, data curation, visualization, writing-review and editing

Konstantinos Tourlakopoulos: resources, data curation, visualization, writing-review and editing

Athanasios Pagonis: resources, data curation, visualization, writing-review and editing

Christos Kampolis: resources, data curation, visualization, writing-review and editing

Luis García De Guadiana Romualdo: resources, data curation, visualization, writing-review and editing

Dimitrios Ragias: resources, data curation, visualization, writing-review and editing

Jesper Eugen-Olsen: methodology, resources, data curation, visualization, writing-review and editing

Konstantinos Gourgoulianis: resources, data curation, visualization, writing-review and editing

Eleni Arnaoutoglou: resources, data curation, visualization, writing-review and editing

Data sharing

Data from SPARCOL can be made available upon request through a collaborative process. Please contact thanoschalkias@yahoo.gr for additional information.

Declaration of Competing Interest

JEO is a co-founder, shareholder and CSO of ViroGates A/S and is mentioned inventor on patients on suPAR owned by Copenhagen University Hospital Hvidovre, Denmark. For the remaining authors none were declared.

Acknowledgements

SPARCOL investigators:

University of Thessaly, Faculty of Medicine, Larisa, Greece: Athanasios Chalkias, Ioannis Pantazopoulos, Anargyros Skoulakis, Eleni Laou, Konstantina Kolonia, Nicoletta Ntalarizou, Maria Mermiri, Anastasia Michou, Dimitrios Ragias, Konstantinos Tourlakopoulos, Athanasios Pagonis, Konstantinos Gourgoulianis, Eleni Arnaoutoglou

Eginition University Hospital, Athens, Greece: Nikolaos Papagiannakis

Hippokrateion University Hospital, Athens, Greece: Christos Kampolis

Evangelismos University Hospital, Athens, Greece: Vasileios Vlachakos, Ioannis Kalomenidis

Hospital Universitario Santa Lucía, Cartagena, Spain: Luis García de Guadiana Romualdo, María Dolores Albaladejo-Otón, María Dolores Rodríguez Mulero, María Galindo Martínez, Marta Hernández Olivo, Valerio Campos Rodríguez.

Hospital Universitario Virgen de la Arrixaca, Murcia, Spain: Iria Cebreiros López, María Arnaldos Carrillo, Jose Antonio Noguera Velasco, Domingo A Pascual Figal.

Hospital General Universitario Reina Sofía, Murcia, Spain: Enrique Bernal Morell, Antonia Alcaraz García, María José Alcaraz García, Monica Martínez Martínez, Patricia Esteban-Torrella, Natalia Sancho-Rodríguez.

Copenhagen University Hospital Hvidovre, Hvidovre, Denmark: Jesper Eugen-Olsen

References

[1] S.P. Etheridge, S.Y. Asaki, COVID-19 infection and corrected QT interval prolongation-collateral damage from our newest enemy, JAMA Netw. Open 4 (2021) e217192.

[2] K. Farsalinos, K. Poulas, D. Kouretas, et al., Improved strategies to counter the COVID-19 pandemic: lockdowns vs. primary and community healthcare, Toxicol. Rep. 8 (2021) 1–9.

[3] D. Calina, T. Hartung, I. Mardare, et al., COVID-19 pandemic and alcohol consumption: impacts and interconnections, Toxicol. Rep. 8 (2021) 529–535.

[4] A.S. Parwani, M. Haug, T. Keller, et al., Cardiac arrhythmias in patients with COVID-19: lessons from 2300 telemetric monitoring days on the intensive care unit, J. Electrocardiol. 66 (2021) 102–107.

[5] R. Challen, E. Brooks-Pollock, J.M. Read, L. Dyson, K. Tsaneva-Atanasova, L. Danon, Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study, BMJ 372 (2021) n579.

[6] Genomic Surveillance Network for SARS-CoV-2 Mutations, 2021 (24-01-2021). https://eody.gov.gr/. Accessed April 3, 2021.

[7] S. Buenestado-Serrano, R. Recio, P.J. Sola Campoy, et al., Gregorio Marañón Microbiology-ID COVID 19 Study Group, 12 de Octubre Microbiology COVID 19 Study Group, La Princesa Microbiology-ID COVID 19 Study Group, Hospital Alcorcón Microbiology-ID COVID 19 Group. First confirmation of importation and transmission in Spain of the newly identified SARS-CoV-2 B.1.1.7 variant, Enferm. Infecc. Microbiol. Clin. (2021), https://doi.org/10.1016/j.eimc.2021.02.006. Epub ahead of print.

[8] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gøtzsche, J.P. Vandenbroucke, STROBE Initiative, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies, BMJ 335 (2007) 806–808.
[9] F. Angeli, A. Spanevello, R. De Ponti, et al., Electrocardiographic features of patients with COVID-19 pneumonia, Eur. J. Intern. Med. 78 (2020) 101–106.
[10] D. Frampton, T. Rampling, A. Cross, et al., Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: a whole-genome sequencing and hospital-based cohort study, Lancet Infect. Dis. (2021), https://doi.org/10.1016/S1473-3099(21)00170-5. Epub ahead of print.
[11] J. Fajnzylber, J. Regan, K. Coxen, et al., SARS-CoV-2 viral load is associated with increased disease severity and mortality, Nat. Commun. 11 (2020) 5493.
[12] The New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG), 2021. Update note on B.1.1.7. severity, 11 February. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/961042/S1095_NERVTAG_update_note_on_B.1.1.7_severity_20210211.pdf. Accessed April 8, 2021.
[13] N. Rovina, K. Akinosoglou, J. Eugen-Olsen, S. Hayek, J. Reiser, E.J. Giamarellos-Bourboulis, Soluble urokinase plasminogen activator receptor (suPAR) as an early predictor of severe respiratory failure in patients with COVID-19 pneumonia, Crit. Care 24 (2020) 187.
[14] T.U. Azam, H.R. Shadid, P. Blakely, et al., International Study of Inflammation in COVID-19. Soluble Urokinase Receptor (SuPAR) in COVID-19-related AKI, J. Am. Soc. Nephrol. 31 (2020) 2725–2735.
[15] P.E. Lazzerini, F. Laghi-Pasini, M. Boutjdir, P.L. Capecchi, Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies, Nat. Rev. Immunol. 19 (2019) 63–64.
[16] K.J. Tracey, The inflammatory reflex, Nature 420 (2002) 853–859.
[17] V.A. Pavlov, H. Wang, C.J. Czura, S.G. Friedman, K.J. Tracey, The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation, Mol. Med. 9 (2003) 125–134.
[18] J.M. Huston, M. Gallowitsch-Puerta, M. Ochani, K. Ochani, R. Yuan, M. Rosas-Ballina, M. Ashok, R.S. Goldstein, S. Chavan, V.A. Pavlov, C.N. Metz, H. Yang, C. J. Czura, H. Wang, K.J. Tracey, Transcutaneous vagus nerve stimulation reduces serum high mobility group box 1 levels and improves survival in murine sepsis, Crit. Care Med. 35 (2007) 2762–2768.
[19] J.M. Huston, K.J. Tracey, The pulse of inflammation: heart rate variability, the cholinergic anti-inflammatory pathway and implications for therapy, J. Intern. Med. 269 (January (1)) (2011) 45–53, https://doi.org/10.1111/j.1365-2796.2010.02321.x. PMID: 21158977; PMCID: PMC4527046.
[20] Y.F. Li, C. LaCroix, J. Freeling, Specific subtypes of nicotinic cholinergic receptors involved in sympathetic and parasympathetic cardiovascular responses, Neurosci. Lett. 462 (October (1)) (2009) 20–23.
[21] Y.F. Li, C. Lacroix, J. Freeling, Cytisine induces autonomic cardiovascular responses via activations of different nicotinic receptors, Auton. Neurosci. 154 (April (1-2)) (2010) 14–19.
[22] V. Lionetti, S. Bollini, R. Coppini, et al., Understanding the heart-brain axis response in COVID-19 patients: a suggestive perspective for therapeutic development, Pharmacol. Res. 168 (2021) 105581.
[23] G. Lagoumintzis, C.T. Chasapis, N. Alexandris, et al., Nicotinic cholinergic system and COVID-19: in silico identification of interactions between α7 nicotinic acetylcholine receptor and the cryptic epitopes of SARS-Co-V and SARS-CoV-2 Spike glycoproteins, Food Chem. Toxicol. 149 (2021) 112009.
[24] N. Alexandris, G. Lagoumintzis, C.T. Chasapis, et al., Nicotinic cholinergic system and COVID-19: in silico evaluation of nicotinic acetylcholine receptor agonists as potential therapeutic interventions, Toxicol. Rep. 8 (2020) 73–83.
[25] R.J. Dekker, J.V. van Thienen, J. Rohlena, et al., Endothelial KLF2 links local arterial shear stress levels to the expression of vascular tone-regulating genes, Am. J. Pathol. 167 (2005) 609–618.
[26] J.A. Nicolás-Ávila, A.V. Lechuga-Vieco, L. Esteban-Martínez, et al., A network of macrophages supports mitochondrial homeostasis in the heart, Cell 18 (2020) 94–109, e23.
[27] A. Chalkias, A. Mouzarou, E. Samara, T. Xanthos, E. Ischaki, I. Pantazopoulos, Soluble urokinase plasminogen activator receptor: a biomarker for predicting complications and critical care admission of COVID-19 patients, Mol. Diagn. Ther. 24 (2020) 517–521.
[28] A. Chalkias, E.F. Barreto, E. Laou, et al., A critical appraisal of the effects of anesthetics on immune-system modulation in critically ill patients with COVID-19, Clin. Ther. 43 (2021) e57–e70.
[29] A. Chalkias, F. Pavlopoulos, E. Papageorgiou, et al., Development and testing of a novel anaesthesia induction/ventilation protocol for patients with cardiogenic shock complicating acute myocardial infarction, Can. J. Cardiol. 34 (2018) 1048–1058.
[30] V. Russotto, S.N. Myatra, J.G. Laffey, et al., INTUBE study investigators. Intubation practices and adverse peri-intubation events in critically ill patients from 29 countries, JAMA 325 (2021) 1164–1172.
[31] A. Chalkias, T. Xanthos, E. Papageorgiou, A. Anania, A. Beloukas, F. Pavlopoulos, Intraoperative initiation of a modified ARDSNet protocol increases survival of septic patients with severe acute respiratory distress syndrome, Heart Lung 47 (2018) 616–621.
[32] A. Chalkias, I. Mamais, T. Xanthos, Microcirculation-mediated preconditioning and intracellular hypothermia, Med. Hypotheses 115 (2018) 8–12.