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Heart rate variability and adrenal size provide clues to sudden cardiac death in hospitalized COVID-19 patients

1. Introduction

There may be an association between Coronavirus Disease 2019 (COVID-19) and sudden cardiac death (SCD), sudden death from a cardiac cause [1]. The etiology of SCD in COVID-19 is not clearly defined and in the absence of precipitating causes such as myocarditis, pulmonary embolism, or acute coronary syndrome, the differential diagnosis may include stress cardiomyopathy refractory to exogenous vasopressors.

Several factors contribute to the difficulty of determining the potential pathomechanism of SCD in COVID-19. Screening and diagnostic procedures such as transthoracic echocardiograms were dramatically decreased [2] (due to risk of COVID-19 exposure to healthcare workers), replaced by reliance on clinical intuition. For example, stress cardiomyopathy has been associated with sudden cardiac death [3] and is typically diagnosed by echocardiogram and coronary catheterization. The role of stress cardiomyopathy or other identifiable etiologies of SCD in hospitalized patients with COVID-19 has not been fully elucidated.

We hypothesized that the cardiac telemetry of inpatients who died with clinically identified SCD would show decreased parasympathetic activity, measured as root mean square of successive differences (RMSSD), consistent with acute stress cardiomyopathy [4]. Given a possible link between stress cardiomyopathy and adrenal insufficiency, [5] we hypothesized that critically ill COVID-19 patients were more likely to have adrenal insufficiency either because of or despite corticosteroid therapy.

2. Methods

We included adult COVID-19 patients admitted to a telemetry-bed at Columbia University Irving Medical Center, who died between 4/25/2020 and 7/14/2020 and had an autopsy.

Clinical criteria for SCD using chart review was: unexplained rapidly progressive cardiovascular collapse (i.e., despite increasing vasopressors) in patients who had stabilized. Three clinicians (2 intensivists [BR and SP] and 1 cardiologist [HY]), blinded to autopsy results, reviewed charts for SCD (Table 1). Disagreement on SCD labels was determined by majority.

RMSSD was generated from ectopy-free, non-overlapping 5-min segments of continuous telemetry, acquired at 240 samples a second from Philips Intellivue MX800 monitors (Amsterdam, Netherlands).

Demographics and comorbidities between groups (non-SCD or SCD) were compared using Wilcoxon rank-sum or Fisher's exact test as appropriate. Mann–Whitney two-sample statistic was used to compare adjusted organ weights between groups (non-SCD and SCD).

This study was approved by the Columbia University Institutional Review Board.

3. Results

Thirty COVID-19 patients were included and 12 had SCD (Table 1). The agreement by pairwise-kappa statistics between SP-HY (0.45) and HY-BR (0.52) was "moderate" while the agreement between SP & BR was "very strong" (0.92). One patient was missing adrenal weights.

Autopsy reports were examined for pulmonary embolism, myocarditis, and coronary artery occlusion or myocardial infarction. In non-SCD patients, three patients had focal mild/borderline lymphocytic myocarditis and one patient had acute myocardial ischemia. One had medium-sized pulmonary artery thrombus and two had non-occlusive thrombus. One had an acute right ventricle infarct. In the SCD patients, one patient had mild ischemic damage to the right ventricle, and one had myocardial infarction occurring at least 3–4 weeks before death. No patients had pulmonary embolism or myocarditis.

The RMSSD over 7 days without vs with SCD was median 0.0129 (IQR 0.0074–0.026) versus 0.0098 (IQR 0.0056–0.0197), $p < 0.0001$ (Fig. 1). All organ weights were equivalent between groups (including heart, lungs, spleen, liver, kidney and thyroid) except for adrenal weights. The total adjusted adrenal weight of the non-SCD group was 0.40 g/kg (IQR 0.35–0.55) versus 0.25 g/kg (IQR 0.21–0.31) in the SCD group, $p = 0.0007$. Four (22%) non-SCD and three (25%) SCD patients received at least 14 days of steroids ≥25 mg of prednisone equivalents in the 30 days prior to death.

4. Discussion

Hospitalized patients with COVID-19 who experienced SCD had lower parasympathetic activity (RMSSD) and smaller sized adrenal glands. Lower RMSSD has been associated with sudden unexplained death in epilepsy (SUDEP) [6], SCD in congenital cardiac disease [7], neurocardiogenic injury in patients with subarachnoid hemorrhage [8], and stress cardiomyopathy [4]. Additionally, COVID-19 patients admitted to the ICU have been shown to have lower RMSSD compared to sepsis patients without COVID-19 admitted to the ICU [9]. Our findings of lower RMSSD in SCD patients could be explained by acute stress cardiomyopathy. Acute stress cardiomyopathy is a clinical/imaging diagnosis, and echocardiograms were limited during the pandemic to minimize exposure [2]. It is notable that the SCD patients had significantly smaller adrenals, suggesting either

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Table 1
Characteristics of patients with and without sudden cardiac death.*

Characteristics	Non-SCD	SCD	*p*-value
N (%)	18 (60%)	12 (40%)	
Age, median (IQR)	73.5 (70–79)	66 (61.5–70.5)	0.007
Female, n (%)	4 (22%)	4 (33%)	0.68
BMI (kg/m2), median (IQR)	27 (24–30)	31 (28–34)	0.059
Chronic kidney disease, n (%)	2 (11%)	3 (25%)	0.36
Hypertension, n (%)	13 (72%)	9 (75%)	0.87
Diabetes Mellitus, n (%)	7 (39%)	2 (17%)	0.25
Asthma, n (%)	1 (6%)	1 (8%)	1.00
COPD, n (%)	2 (11%)	1 (8%)	1.00
Hyperlipidemia, n (%)	5 (28%)	3 (25%)	1.00
Stroke	(0%)	1 (8%)	0.40
HIV, n (%)	0 (0%)	1 (8%)	0.40
HFrEF, n (%)	2 (11%)	0 (0%)	0.50
CAD, n (%)	3 (17%)	0 (0%)	0.26

* No end-stage renal disease nor heart failure with preserved ejection fraction in either group.

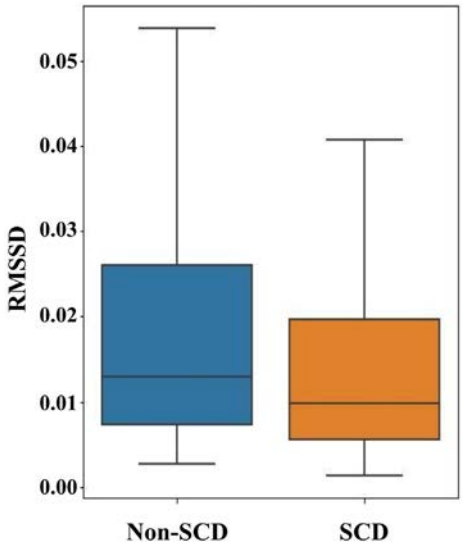

Fig. 1. RMSSD for patients with and without sudden cardiac death.
Median RMSSD was significantly lower in patients with sudden cardiac death (SCD) compared to patients without SCD ($p < 0.0001$).

adrenal atrophy from steroids or lack of adrenal hyperplasia in response to prolonged critical illness. The smaller adrenal gland size coupled with stress cardiomyopathy may have led to refractory cardiovascular collapse. Further work is needed to confirm these findings in additional cohorts.

4.1. Limitations

This retrospective case-control study enrolled patients who had autopsies ordered by the clinicians, a potential source of selection bias. Additionally, the definition of sudden cardiac death has some subjectivity.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

References

[1] Contou D, Cally R, Sarfati F, Desaint P, Fraisse M, Plantefeve G. Causes and timing of death in critically ill COVID-19 patients. Crit Care. 2021;25(1):79. https://doi.org/10.1186/s13054-021-03492-x.
[2] Ward RP, Lee L, Ward TJ, Lang RM. Utilization and appropriateness of transthoracic echocardiography in response to the COVID-19 pandemic. J Am Soc Echocardiogr. 2020;33(6):690–1. https://doi.org/10.1016/j.echo.2020.04.006.
[3] Gili S, Cammann VL, Schlossbauer SA, Kato K, D'Ascenzo F, Di Vece D, et al. Cardiac arrest in takotsubo syndrome: results from the InterTAK registry. Eur Heart J. 2019;40(26):2142–51. https://doi.org/10.1093/eurheartj/ehz170.
[4] Otak J, Khattab K, Barantke M, Wiegand UKH, Bänsch D, Ince H, et al. Evolution of cardiac autonomic nervous activity indices in patients presenting with transient left ventricular apical ballooning. Pacing Clin Electrophysiol. 2009;32(s1). https://doi.org/10.1111/j.1540-8159.2008.02221.x. S21-S5.
[5] Gupta S, Goyal P, Idrees S, Aggarwal S, Bajaj D, Mattana J. Association of endocrine conditions with takotsubo cardiomyopathy: a comprehensive review. J Am Heart Assoc. 2018;7(19):e009003. https://doi.org/10.1161/JAHA.118.009003.
[6] DeGiorgio CM, Miller P, Meymandi S, Chin A, Epps J, Gordon S, et al. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: the SUDEP-7 inventory. Epilepsy Behav. 2010;19(1):78–81. https://doi.org/10.1016/j.yebeh.2010.06.011.
[7] Lammers A, Kaemmerer H, Hollweck R, Schneider R, Barthel P, Braun S, et al. Impaired cardiac autonomic nervous activity predicts sudden cardiac death in patients with operated and unoperated congenital cardiac disease. J Thorac Cardiovasc Surg. 2006;132(3):647–55. https://doi.org/10.1016/j.jtcvs.2006.03.057.
[8] Megjhani M, Kaffashi F, Terilli K, Alkhachroum A, Esmaeili B, Doyle KW, et al. Heart rate variability as a biomarker of neurocardiogenic injury after subarachnoid hemorrhage. Neurocrit Care. 2020;32(1):162–71. https://doi.org/10.1007/s12028-019-00734-3.
[9] Kamaleswaran R, Sadan O, Kandiah P, Li Q, Coopersmith CM, Buchman TG. Altered heart rate variability early in ICU admission differentiates critically ill coronavirus disease 2019 and all-cause Sepsis patients. Crit Care Explor. 2021;3(12):e0570. https://doi.org/10.1097/CCE.0000000000000570.

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