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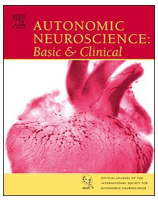

Short communication

Syncope at SARS-CoV-2 onset

Ciro Canetta[a], Silvia Accordino[a], Elisabetta Buscarini[b], Gianpaolo Benelli[c], Giuseppe La Piana[d], Alessandro Scartabellati[e], Giovanni Viganò[f], Roberto Assandri[g], Alberto Astengo[h,i], Chiara Benzoni[h,i], Gianfranco Gaudiano[h,i], Daniele Cazzato[j], Davide Sebastiano Rossi[j], Susanna Usai[i], Irene Tramacere[k], Giuseppe Lauria[h,i,*]

[a] Emergency Medicine Unit, Ospedale Maggiore di Crema, Crema, Italy
[b] Gastroenterology Unit, Ospedale Maggiore di Crema, Crema, Italy
[c] Radiology Unit, Ospedale Maggiore di Crema, Crema, Italy
[d] Pneumology 2 Unit, Ospedale Maggiore di Crema, Crema, Italy
[e] Pneumology 1 Unit, Ospedale Maggiore di Crema, Crema, Italy
[f] Emergency Unit, Ospedale Maggiore di Crema, Crema, Italy
[g] Clinical Investigation Laboratory, Ospedale Maggiore di Crema, Crema, Italy
[h] Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Milan, Italy
[i] Department of Clinical Neurosciences, Neuroalgology Unit, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy
[j] Department of Diagnostics and Technology, Clinical Neurophysiology Unit, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy
[k] Scientific Directorate, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy

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ABSTRACT

We describe clinical and laboratory findings in 35 patients tested positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction on nasopharyngeal swab experiencing one or multiple syncope at disease onset. Clinical neurologic and cardiologic examination, and electrocardiographic findings were normal. Chest computed tomography showed findings consistent with interstitial pneumonia. Arterial blood gas analysis showed low pO_2, pCO_2, and ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) indicating hypocapnic hypoxemia. Patients who presented with syncope showed significantly lower heart rate as compared to 68 SARS-CoV-2 positive that did not. Such poorer than expected compensatory heart rate increase may have led to syncope based on individual susceptibility.

We speculate that SARS-CoV-2 could have caused angiotensin-converting enzyme-2 (ACE2) receptor internalization in the nucleus of the solitary tract and other midbrain nuclei, impairing baroreflex and chemoreceptor response, and inhibiting the compensatory tachycardia during acute hypocapnic hypoxemia.

Since the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in Italy on February 19th, 2020, the Lombardy Region in Northern Italy has been one the most affected areas in Europe. The public hospital in the town of Crema was one of the first to face the exponential influx of patients. Thanks to the immediate adoption of available local procedures to cope with the hospitalization of patients with a potential viral spread, based on 2009 SARS and H1N1 pandemic strategic plan revised on December 2014 after Ebola outbreak, the Emergency Department could set up a standardized triage for any individual either reporting or presenting with fever, cough, or dyspnea, or having had contact with potentially COVID-19 carriers. Since February 21th, all consecutive suspected patients admitted to the hospital underwent a procedure including body temperature and pulse oximetry (SO_2) recording, hematological screening, chest X-ray and/or computed tomography (CT) scan, and nasopharyngeal swab. Swabs were stored at +4 °C and immediately shipped to one of the laboratory of virology accredited by the Lombardy Region to perform diagnostic SARS-COV-2 real-time polymerase chain reaction (RT-PCR) assay. Based on the clinical, laboratory, and radiological findings, patients were discharged to home in quarantine or admitted to the hospital.

Recently, some case series have reported syncope as the first manifestation of SARS-CoV-2 infection, even in the absence of other common symptoms such as fever, cough, and dyspnea (Ebrille et al.,

* Corresponding author at: Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan and Department of Clinical Neuroscience, Neuroalgology Unit, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy.
E-mail address: giuseppe.lauriapinter@istituto-besta.it (G. Lauria).

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Table 1
SARS-Cov-2 patients presenting with syncope initial features. SO_2 is oxygen saturation; pCO_2 and pO_2 are partial pressure of CO_2 and O_2; FiO_2 is fraction of inspired oxygen; PaO_2/FiO_2 is the ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2); MAP is mean arterial pressure calculated as [diastolic + 1/3(systolic − diastolic)]. Angiotensin-converting enzyme (ACE); angiotensin II receptor blockers (ARB). Mean heart rate was significantly lower in syncope group both considering all patients (*$p < 0.02$; unpaired *t*-test) and those not taking beta-blockers (**$p < 0.01$; unpaired *t*-test).

	Patients with syncope (n = 35)	Patients without syncope (n = 68)
Age, years		
Mean (SD)	74 (12)	72 (12)
Median (range)	76 (44–93)	73 (35–99)
Sex, n (%)		
Male	24 (69%)	51 (75%)
Female	11 (31%)	17 (25%)
Repeated syncope, n (%)	9 (26%)	–
SO_2		
Mean (SD)	94 (8)	92 (5)
Median (range)	96 (52–99)	93 (75–99)
pCO_2		
Mean (SD)	32 (40)	33 (7)
Median (range)	32 (21–40)	33 (17–65)
$pCO_2 < 35$, n (%)	27 (77%)	47 (70%)
pO_2		
Mean (SD)	64 (8)	63 (14)
Median (range)	64 (51–81)	62 (32 − 120)
$pO_2 < 60$, n (%)	12 (34%)	27 (40%)
FiO_2		
Mean (SD)	0.23 (0.05)	0.26 (0.14)
Median (range)	0.21 (0.21–0.40)	0.21 (0.21–0.9)
PaO_2/FiO_2		
Mean (SD)	284 (60)	266 (65)
Median (range)	289 (139–379)	274 (80–375)
P/F ≤ 300, n (%)	20 (57%)	43 (64%)
Heart rate (all patients)		
Mean (SD)*	87 (17)	95 (16)
Median (range)	88 (50–120)	94 (58–140)
FC > 100, n (%)	6 (17%)	19 (28%)
Heart rate (no beta-blocker)		
Mean (SD) **	84 (15)	96 (16)
Median (range)	82 (50–120)	93 (58–140)
FC > 100, n (%)	5 (15%)	17 (34%)
MAP		
Mean (SD)	90 (16)	93 (14)
Median (range)	87 (56–133)	93 (56–129)
Drugs		
ACE inhibitors/ARB	41.4%	44%
Beta-blockers	31.4%	26.5%
Neuroleptic	6.2%	7.3%

2020; Tape et al., 2020). Patients had in common comorbidities for heart disease, coronary artery disease, post-permanent pacemaker (PPM) or cardiac loop recorder implantation (Ebrille et al., 2020; Tape et al., 2020). We analyzed 411 consecutive patients tested positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction at nasopharyngeal swab among whom nearly 10% reported syncope at the onset of the infection (Benelli et al., 2020). Herewith we describe clinical and laboratory findings in 35 consecutive patients of whom all data were available that presented one or multiple (9 patients; 25.7%) syncopal events at disease onset. Findings were compared with those from 68 SARS-CoV-2 patients who did not experience any syncope and were admitted during the same period. Demographic data, functional respiratory findings, and mean arterial pressure values, did not differ between the two groups. Conversely, mean heart rate was significantly lower in patients who experienced syncope (Table 1).

Syncope occurred within 3.6 ± 2.7 days from hospital admission. Nine (25.7%) patients reported head trauma and one subdural haemorrhage. Associated onset symptoms were fever > 37.5 °C in 17 (48.5%) patients, cough in 8 (22.8%), and dyspnoea in 7 (20%). Hypertension (45.7%), dyslipidaemia (17%), renal insufficiency (20%), hypothyroidism (5.7%), dementia (11.4%), cancer (11.4%), and atrial fibrillation (5.7%) were the most common comorbidities. Besides the personal history of first-ever syncope, no other signs of dysautonomia were reported. Among patients not reporting any syncope, onset symptoms were fever > 37.5 °C in 48 (70.6%) patients, cough in 27 (39.7%), and dyspnoea in 21 (31%). Hypertension (42.6%), cancer (8.4%), renal insufficiency (7.4%), and atrial fibrillation (4.4%) were the most common comorbidities. The distribution of drugs potentially interfering with the heart rate was also similar between the groups (Table 1).

The neurological examination was normal in all patients. Chest computed tomography showed single or multiple ground-glass and/or consolidative lung opacities consistent with interstitial pneumonia in all patients. Patients reporting syncope had normal clinical cardiac assessment. Consistently, their electrocardiogram showed corrected QT interval at rest ranging 409–511 ms (mean 451 ± 30; median 449.5; interquartile range 433–474), PR interval ranging 104–220 ms (mean 161 ± 35.5; median 153; interquartile range 136.5–195.5), and QRS complex duration ranging 66–134 ms (mean 95 ± 18; median 93; interquartile range 83–105.5), which were nearly within normal values. These findings made unlikely that patients suffered from a cardiomyopathy and sinus node disease related to the SARS-COV-2, which however was not systematically assessed.

Initial arterial blood gas analysis showed low pO_2, pCO_2, and ratio of arterial oxygen partial pressure (in mmHg) to fractional inspired oxygen (PaO_2/FiO_2) which was consistent with a hypocapnic hypoxemia condition in most patients, with no difference between patients who reported syncope and those who did not (Table 1). However, patients with syncope showed a significantly lower compensatory heart rate increase, which could explain the clinical episodes (Yasuma and Hayano, 2000). This difference remained significant when patients not taking beta-blockers in the two groups were analyzed (Table 1), thus strengthening the pathophysiological hypothesis.

Cardiovascular and respiratory systems strongly interact to ensure adequate oxygen release to tissues and organs in response to systemic variability under the control of two integrated pathways: central baroreception and chemoreception. The balance between sympathetic and parasympathetic inputs predominantly regulates heart rate response through the baroreflex control. The increased compensatory tachycardia response to hypoxia induces higher cardiac output, while stroke volume remains unchanged. Central chemoreception, besides detecting brain blood flow and metabolism and acid-base balance, alters the sympathetic tone in response to arterial PCO_2 changes. The baroreceptor reflex control of heart rate is regulated by the brain renin–angiotensin system mainly in the nucleus of the solitary tract (NTS) of the brainstem, where ACE2 is expressed (Doobay et al., 2007; Xia and Lazartigues, 2010). The chemoreception system has a wider nuclear involvement in the hindbrain, including the NTS (Nattie and Li, 2012).

SARS-CoV-2 viral coat expresses the spike protein that contains a receptor-binding region with high affinity for the extracellular domain of angiotensin-converting enzyme-2 (ACE2) receptor. Binding leads to ACE2 internalization. It has been shown that the loss of ACE2 at cell surface could precipitate existing cardiovascular, kidney and brain diseases (South et al., 2020). In patients experiencing syncope, SARS-CoV-2 could have caused ACE2 internalization in the NTS and other midbrain nuclei, thus altering the baroreflex and chemoreceptor responses, and partly inhibiting the compensatory increase of heart rate during acute hypocapnic hypoxemia. The causes of such individual susceptibility are unknown. However, this hypothesis finds support from some preclinical evidence. ACE2 in the NTS is required to maintain the normal sensitivity of the baroreflex control on heart rate (Xia and Lazartigues, 2010) and the experimental injection of ACE2 antagonist in the NTS reduced the baroreceptor response for reflex bradycardia (Diz et al., 2008). We speculated that individual patients with specific susceptibility developed an impaired response of baroreceptors

and chemoreceptors to endogenous stimuli which led to the occurrence of syncope.

References

Benelli, G., Buscarini, E., Canetta, C., La Piana, G., Merli, G., Scartabellati, A., Viganò, G., Sfogliarini, R., Melilli, G., Assandri, R., Cazzato, D., Rossi, D.S., Usai, S., Caldarelli, G., Gili, T., Tramacere, I., Pellegata, G., Lauria, G., 2020. SARS-COV-2 Comorbidity Network and Outcome in Hospitalized Patients in Crema, Italy. https://doi.org/10.1101/2020.04.14.20053090.

Diz, D.I., Garcia-Espinosa, M.A., Gegick, S., Tommasi, E.N., Ferrario, C.M., Ann Tallant, E., Chappell, M.C., Gallagher, P.E., 2008. Injections of angiotensin-converting enzyme 2 inhibitor MLN4760 into nucleus tractus solitarii reduce baroreceptor reflex sensitivity for heart rate control in rats. Exp. Physiol. 93, 694–700.

Doobay, M.F., Talman, L.S., Obr, T.D., Tian, X., Davisson, R.L., Lazartigues, E., 2007. Differential expression of neuronal ACE2 in transgenic mice with overexpression of the brain renin-angiotensin system. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R373–R381.

Ebrille, E., Lucciola, M.T., Amellone, C., Ballocca, F., Orlando, F., Giammaria, M., 2020. Syncope as the presenting symptom of COVID-19 infection. HeartRhythm Case Rep. 6 (7), 363–366 (May 5).

Nattie, E., Li, A., 2012. Central chemoreceptors: locations and functions. Compr. Physiol. 2, 221–254.

South, A.M., Diz, D.I., Chappell, M.C., 2020. COVID-19, ACE2, and the cardiovascular consequences. Am. J. Physiol. Heart Circ. Physiol. 318, H1084–H1090.

Tape, C., Byrd, K.M., Aung, S., Lonks, J.R., Flanigan, T.P., Rybak, N.R., 2020. COVID-19 in a patient presenting with syncope and a normal chest X-ray. R. I. Med. J. 103 (2013), 50–51.

Xia, H., Lazartigues, E., 2010. Angiotensin-converting enzyme 2: central regulator for cardiovascular function. Curr. Hypertens. Rep. 12, 170–175.

Yasuma, F., Hayano, J.I., 2000. Impact of acute hypoxia on heart rate and blood pressure variability in conscious dogs. Am. J. Physiol. Heart Circ. Physiol. 279, H2344–H2349.