Journal of Heart

Case Report | Vol 2 Sp. Iss 2

Unusual Cause of Asystole: An Abnormal Reflex Response to Cough due to Analgo-Sedation

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Received Date: July 22, 2021; **Accepted Date:** July 31, 2021; **Published Date:** August 7, 2021

ABSTRACT

A 53-years-old woman, hospitalized in the intensive care unit for an acute respiratory distress syndrome due to SARS-CoV-2 infection, presented multiples episodes of deep bradycardia and asystole while intubated and sedated. These episodes were resolved once the patient was extubated. We hypothesize that these rhythm disorders were induced by an imbalance between the parasympathetic nervous system stimulated by coughing and the sympathetic nervous system inhibited by sedation. The possibility of dysautonomia related to Covid infection is also raised. This is a diagnosis by exclusion, so other etiologies of bradycardia or asystole were sought.

KEYWORDS

Cardiology; Rhythm; Asystole; Bradycardia; Covid-19

INTRODUCTION

We describe the case of a 53-year-old woman, hospitalized in the intensive care unit for an acute respiratory distress syndrome due to SARS-CoV-2 infection, who presented multiples episodes of deep bradycardia and asystole while intubated and sedated. These episodes were resolved once the patient was extubated.

We hypothesize that these rhythm disorders were induced by an imbalance between the parasympathetic nervous system stimulated by coughing and the sympathetic nervous system inhibited by sedation. The possibility of dysautonomia related to Covid infection is also raised.

CASE REPORT

A 53-year-old woman patient was admitted to the intensive care unit with severe acute respiratory distress syndrome due to SARS-CoV-2 infection.

She was intubated and put on invasive mechanical ventilation. She benefited from a multimodal analgo-sedation including propofol (up to 400 mg/h), ketamine (up to 50 mg/h) fentanyl (up to 150 mcg/h) and midazolam (up to 5mg/h). Whenever the nurse performed tracheal aspirations, the patient presented reflex cough systematically associated with deep sinus bradycardia and two episodes of asystole (Figure 1). The beta-agonist drug Isoprenaline was introduced and titrated for a heart

Citation: Baudouin Bourlond, Unusual Cause of Asystole: An Abnormal Reflex Response to Cough due to Analgo-sedation. J Heart 2(S2): 36-41.

rate of 100 bpm which prevented new episodes of asystole but did not completely eliminate the bradycardia associated with the cough. Isoprenaline therapy was well tolerated, without associated hypotension or new rhythm disturbances. The respiratory evolution was positive and the patient could be extubated after 7 days.

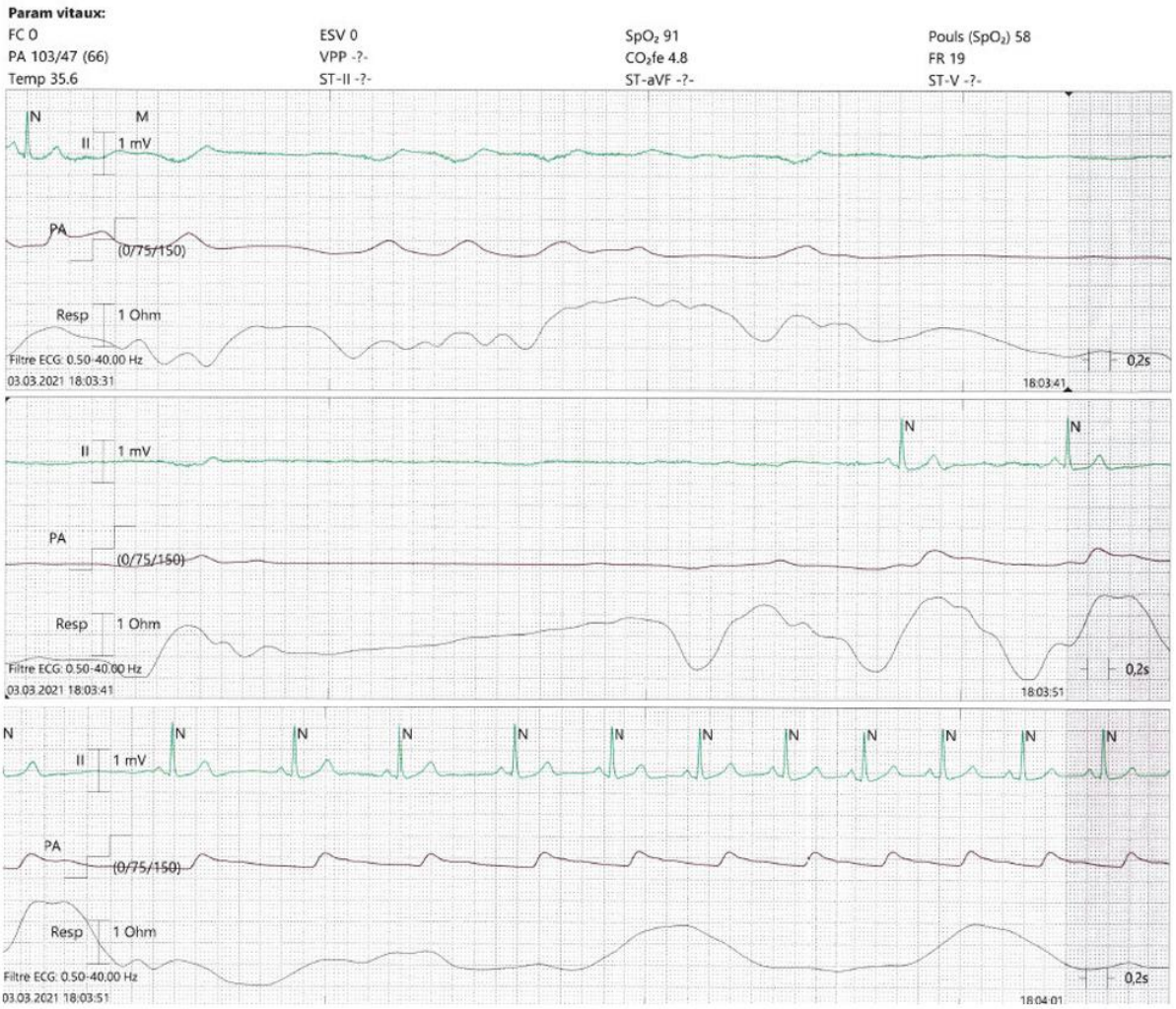

Figure 1: The monitoring reveals an asystole of 19 seconds. The green line shows the absence of heartbeat and the red line shows the absence of pulsation of the radial artery.

After extubation, she never presented bradycardia nor asystole again.

The patient had no previous history of syncope, rhythm disorder or heart disease. She has no relevant medical history unless a possible Vogt-Koyanagi-Harada syndrome (VKH) and a class II obesity (BMI 38.2 kg/m2).

The patient was discharged from the ICU on day 10 and she returned home 4 days later.

DISCUSSION

There are multiple hypotheses to explain the bradycardia and asystole episodes of this patient.

There are hundreds of manuscripts describing cough-induced syncope, a diagnosis first communicated by Charcot in 1876 [1]. In the past 25 years (1988–2013), 40 articles reported cough syncope and provided gender data. There is a majority of male with 91.6% of the patients compared to only 8.4% who were female [2].

Cough, whether continuous or intermittent, leads to multiple pathophysiological processes of the neurologic and cardiovascular systems.

Cough can lead to a greater rise in intrathoracic pressure, decreasing venous return and cardiac output and consequently causing cerebral hypoperfusion.

Cerebrospinal fluid (CSF) pressure rises to essentially the same level as intrathoracic pressure when coughing. This has led some authors to suggest that increased CSF pressure, by increasing intracranial pressure, causes blood to be "squeezed", rapidly causing hypoperfusion, with subsequent anoxia and syncope.

On the other hand, cough is also associated with an acute rise in systemic arterial pressure for which a baroreflex response with parasympathetic activation and sympathetic inhibition is expected. The consequence will be a subsequent decrease in heart rate, cardiac contractility, vascular resistance and venous return [3].

More recent mechanistic studies suggest a neurally mediated reflex vasodepressor-bradycardia response to cough [4-8].

This patient, while in intensive care, received several drugs to be sedated and tolerate the endotracheal tube and mechanical ventilation. All these drugs have various cardiovascular and neurological effects and can interact with the sympathetic and parasympathetic systems.

Propofol (2,6-diisopropylphenol) is a potent intravenous hypnotic drug. It is the most commonly used intravenous anaesthetic for the past decades. It has been proven to be effective and useful for sedation of patients in the intensive care unit.

Propofol is a γ-aminobutyric acid (GABA) receptor agonist. The cardiovascular adverse effects are bradycardia and hypotension.

Midazolam is a benzodiazepine drug commonly used in anesthesia. The effects of the benzodiazepines result from their actions on the ionotropic GABAA receptors in the central nervous system. Midazolam is preferred over other benzodiazepines because of its water solubility and rapid clearance. The cardiovascular adverse effects are hypotension and bradycardia, which could lead to cardiac arrest. These adverse effects occur mainly with rapid injection or high infusion doses.

Ketamine is as an antagonist of the N-methyl-D-aspartate receptor and it has no affinity for gamma-aminobutyric acid receptors in the central nervous system. Ketamine produces hemodynamically stable anesthesia via central sympathetic stimulation [9]. The cardiovascular adverse effects are tachycardia and hypertension.

Fentanyl is a synthetic opioid analgesic commonly prescribed in the intensive care unit (ICU) for its ability to provide both analgesia and sedation to critically ill patients [10]. It exerts his pharmacological action through interaction with the μ-opioid receptor.

The catecholamine that we used to prevent episodes of extreme bradycardia and asystole in this patient was isoprenaline. Isoprenaline is a non-selective β-adrenergic agonist. It stimulates de sympathetic drive with positive inotropic and chronotropic effects, increasing cardiac output by increasing the heart rate and cardiac contractility. Isoprenaline also decreases diastolic blood pressure by lowering peripheral vascular resistance. One of its cardiovascular side effects is tachycardia.

Moreover, cardiovascular manifestations are frequent in COVID-19 patients and high-grade atrioventricular conduction blocks have been described in some of them [11,12].

Neurological manifestations are also common in hospitalized patients with COVID-19. A wide variety of neurological symptoms may occur during COVID-19 infection that may be related to direct damage of neurologic tissues or indirectly due to cytokine release, respiratory insufficiency, critical illness, and side effects of pharmacologic treatment. In a published review of patients hospitalized for SARS-CoV-2 infection, up to 57.4% of patients developed at least one neurologic symptom, but dysautonomia is described in only 2.5% [13].

Current literature on autonomic dysfunction in SARS-CoV-2 infected patients remains very sparse otherwise.

Reiner Buchhorn et al. [14] describe a case of heart rate variability in a non-hospitalized patient. Deepalakshmi Kaliyaperumal et al. [15] conducted a study showing increased parasympathetic tone in SARS-CoV-2 infected patients, independent of important confounders such as diabetes.

Sinus bradycardia and asystole in our patient are suspected to be the direct and immediate result of cough-induced parasympathetic stimulation after endotracheal manipulation, in the context of sympathetic inhibition by ongoing analgo-sedatives drugs. The fact that extubation eliminated these episodes reinforces this hypothesis.

However, prompt evaluation and exclusion of other etiologies was essential.

The patient had no carotid bruit and the neurologic status was in the standard. The carotid sinus massage was negative. The ECG of our patient showed sinusal rhythm without abnormality. Except the bradycardia and asystole episodes, the cardiac scope did not revealed arrhythmia while she was in the intensive care unit. Transthoracic echocardiography showed a left ventricular ejection fraction of 65% without valvular disease, hypertrophy, or other abnormalities.

Obstructive sleep apnea (OSA) serves as a risk factor for cardiovascular diseases, including arrhythmias. (16). Despite being obese, our patient was not known for OSA and no episodes of apnea were observed during her hospitalization in intensive care.

As the patient was in generally good health and the bradycardia/asystole disappeared after she woke up, we did not get brain imaging to exclude brain tumor.

In our case, we hypothesize that analgo-sedation depressed the sympathetic nervous system and that Covid-induced autonomic dysfunction may have played a role. When the patient coughed due to airway manipulations, an imbalance occurred between the stimulated parasympathetic system and the inhibited sympathetic system leading to bradycardia and asystole.

To our knowledge, it is the first case described in an intubated Covid-19 patient. After extubation, all sedation was discontinued and no new episodes of bradycardia or asystole occurred, probably because the sympathetic nervous system was no longer inhibited.

As the patient had never presented that kind of symptoms before intubation and did not have a new episode after extubation, we postulate that it is not exactly the same physiopathology as the well-known “cough induced syncope” described upward.

In our opinion, the patient's episodes of bradycardia and asystoles were induced by a transient imbalance between the sympathetic and parasympathetic nervous system. The influence of Covid-related dysautonomia must also be considered.

CONCLUSION

We hypothesize that over-inhibition of the sympathetic nervous system relative to stimulation of the parasympathetic nervous system could result in deep bradycardia and asystole. And we wonder whether SARS-CoV-2 infection may have played a role in this case.

This is a diagnosis by exclusion, so other etiologies of bradycardia or asystole should be sought.

This hypothesis should be confirmed by other similar case report.

A further fascinating question is whether all individuals are vulnerable to cough-induced bradycardia or asystole under certain threshold conditions.

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