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Letter to the Editor

COVID-19 Pandemic and Angina Pectoris: What If the Pain Pathway Is Pharmaceutically Modulated?

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Dear Editor,

We read with interest the article by Song and colleagues referring to the symptoms of patients infected by the new SARS-CoV2 virus in the early phase of the COVID-19 pandemic [1]. Pain was a characteristic symptom of the patients presented, while some of them expressed chest pain mimicking angina pectoris. Patients with cardiovascular diseases are extremely vulnerable to the attacks of the new virus. In particular, those with ischemic heart diseases and heart failure (HF), when infected, present high morbidity and mortality. The aforementioned risks are increased when elderly patients with diabetes mellitus are concerned. For this reason, the worldwide recommendation for these patients is to remain in prolonged lockdown and quarantine if they come in contact with people infected by COVID-19.

Typical symptoms of COVID-19 virulence are fever, cough, sore throat, fatigue, pain, and dyspnea. The last two represent major diagnostic criteria requiring rapid medical assistance. Thoracic pain can be attributed to various causes. Pneumonia, pleurisy, pulmonary embolism, and cardiac ischemia, including acute myocardial infarction, are just a few culprits in COVID-19 patients, although they share common characteristics, making the diagnosis difficult. Angina pectoris represents the clinical manifestation of myocardial ischemia when the degree of damage surpasses the pain threshold of the patient. Despite the dramatic nature of the pain, this is sometimes a beneficial symptom in the sense that it prompts seeking of medical advice.

An intriguing fact in the case of COVID-19 is that the number of cardiovascular patients visiting emergency departments shows a paradoxical decline [2]. It appears that painful episodes of myocardial ischemia have suddenly decreased, being replaced by silent ischemic attacks. Various explanations for this phenomenon have been proposed. It has been suggested that the reduced atmospheric pollution combined with the reduced professional stress related to quarantine contribute to reduced manifestation of major ischemic episodes. Other observers have attributed the paradox to a COVID-19 phobia, implying that patients with angina pectoris are unwilling to attend emergency departments due to their fear of virus contagion. There are other theories attributing the missing emergency visits of ischemic cardiac patients to a reduced perception of cardiac pain. For example, elderly patients with diabetic neuropathy and dementia have altered cognitive performance and diminished pain perception. This is more so if general anesthesia has been used in the past, as in a previous coronary artery bypass operation, where pain perception has been compromised, leading to silent ischemia. Painless or asymptomatic cardiac ischemia is a dangerous condition because it increases morbidity and mortality by 35% in relation to symptomatic manifestation. The danger is further increased if the accompanying dyspnea, which represents angina equivalent, is missing.

We would like at this point to focus on an overlooked factor of reduced perception of cardiac pain. This is related to some modern pharmaceutical therapies that

cardiovascular patients receive, which modulate the pain pathway. We are referring to the novel compound of sacubitril/valsartan (S/V), which is a rapidly expanding treatment in HF patients since 2014, when this combination was established [3]. It has been estimated that 45–65% of HF patients with reduced ejection fraction worldwide are receiving the S/V combination, which relative to other pharmaceutical treatments impressively reduces morbidity, hospital readmission rates, and mortality. Given the fact that almost half of HF patients also suffer from myocardial ischemia, S/V has widespread application in patients with cardiovascular diseases. Valsartan is an angiotensin receptor antagonist, while sacubitril is a neprilysin (NEP) inhibitor. S/V forms the prototype of angiotensin receptors and NEP inhibitors (ARNIs), giving origin to a novel and prominent class of drugs. Although in the past there were other forms of NEP inhibitors, they have not survived the test of time [4].

NEP, also known as enkephalinase, is a ubiquitous metalloprotease that among other substrates degrades natriuretic peptides and endogenous opioids, namely enkephalins and endorphins [5]. Sacubitril, by inhibiting NEP, increases the circulation of natriuretic peptides, achieving a favorable hemodynamic profile. At the same time, enkephalins and endorphins, which are known antinociceptive compounds, are released, modulating the perception of pain because of their morphine-like properties [6]. Enkephalins and endorphins are ligands to their cognate receptors called opioid receptors, found in the heart, lungs, brain, and other organs. The analgesic action of NEP inhibitors in angina pectoris has been well recognized for at least 30 years [7]. More recently, it has been observed that endorphins reduce the symptom of dyspnea in HF patients treated with S/V, further confirming the role of endogenous opioids as antinociceptive agents [8].

In the COVID-19 era, patients with ischemic heart disease and/or HF belong to the most vulnerable patient groups. In case of coronavirus infection and consequent silent ischemia, a major symptom requiring urgent medical assistance will be missing. Factors relating to the pain threshold, the anatomical integrity of the pain pathway, and pharmaceutical treatment will influence the pain perception of these patients. NEP inhibitors are well-recognized pain modulators and should be taken into consideration when cardiovascular patients are faced with viral infections. We further thank Song and colleagues for giving us the opportunity to shed some light on factors modulating cardiac pain in the context of COVID-19.

References

1. Song XJ, Xiong DL, Wang ZY, Yang D, Zhou L, Li RC. Pain management during the COVID-19 pandemic in China: Lessons learned. Pain Med 2020;XXX(X):XXX–XX.
2. Rosenbaum L. The untold toll-the pandemic's effects of patients without COVID-19. N Engl J Med 2020;382(24):2368–71.
3. McMurray JJ, Packer M, Desai A, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371(11):993–1004.
4. Siniorakis E, Arvanitakis S, Konstantopoulou G, Katechalidou L, Limberi S. Neprilysin inhibitors and chest pain perception in acute myocardial infarction. Geriatr Gerontol Int 2019;19(8):840–1.
5. Bayes-Genis A, Barallat J, Richards AM. A test in context: Neprilysin: Function, inhibition, and biomarker. J Am Coll Cardiol 2016;68(6):639–53.
6. Thanawala V, Kadam VJ, Ghosh R. Enkephalinase inhibitors: Potential agents for the management of pain. Curr Drug Targets 2008;9(10):887–94.
7. Droste C, Roskamm H. Pain perception and endogenous pain modulation in angina pectoris. Adv Cardiol 1990;37:142–64.
8. Revuelta-Lopez E, Nuñez J, Gastelurrutia P, et al. Neprilysin inhibition, endorphin dynamics, and early symptomatic improvement in heart failure: A pilot study. ESC Heart Fail 2020;7(2):559–66.