(reviewed by Fang et al\textsuperscript{11}). It has been reported to have an antiviral effect against SARS CoV-2.\textsuperscript{12} Several reports have shown beneficial responses using inhaled NO therapy in COVID-19 patients.\textsuperscript{13,14} Atopic asthmatic patients have higher inducible NO synthase and exhaled NO, which correlate with sputum eosinophil levels.\textsuperscript{15} Kimura et al\textsuperscript{16} reported reduction of angiotensin-converting enzyme 2 gene expression in asthmatic patients with the Th2 phenotype. Thus, could the connection between the Th2 phenotype and exhaled NO contribute to less severe COVID-19 in asthmatic patients?\textsuperscript{17}

Contributions to endotheliopathy of factors antecedent to infection versus the infection itself remain inconclusive. Certainly, risk and genetic factors can increase susceptibility to endothelial damage upon infection. However, hyperinflammatory and a disordered humoral response to SARS-CoV-2 infection itself significantly contribute to severe COVID-19.

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Proposal for a new classification of respiratory urticaria/angioedema

To the Editor:

We have read with interest the article published by Kulthanan et al\textsuperscript{1} regarding the results of the systematic literature review on vibratory angioedema. The article shows a complete analysis of the published literature and proposes a classification of vibratory angioedema in 2 variants, namely hereditary and acquired. According to the authors, the hereditary forms significantly show wheals compared with the acquired forms.

Hereditary vibratory angioedema was originally described in 1972 by Patterson et al\textsuperscript{2} in a family whose members were diagnosed with angioedema on vibratory stimuli shortly after they were born. Boyden et al\textsuperscript{3} described several members of 3 Lebanese families carrying the ADGRE2 (adhesion G protein-coupled receptor E2) mutation in whom hives on vibratory stimuli predominated in the clinical picture and referred to the condition as vibratory urticaria. These authors intended to study the ADGRE2 mutation in Patterson’s family members but were unable to contact them. In their opinion, based on the clinical manifestations, Patterson’s patients and their own likely suffered from different conditions.\textsuperscript{4,5} Both being hereditary, in Patterson’s cases, lesions consisted of cutaneous/subcutaneous angiodema-tous lesions lasting hours to days,\textsuperscript{2} and in Boyden’s cases, lesions consisted of evanescent hives lasting less than 1 hour.\textsuperscript{3,5} Thus, we propose to subclassify the hereditary variants into 2 subtypes: the hereditary vibratory angioedema (Patterson type) and the hereditary ADGRE2-related vibratory urticaria (Boyden type).

Regarding the acquired cases, they could be subclassified into 2 subtypes: the more frequent acquired vibratory angioedema, characterized by a sustained history of angioedema on vibratory stimuli without hives that may last months or years, and the rare secondary acquired vibratory urticaria,\textsuperscript{6,7} described only twice in relation to Candida glabrata infection\textsuperscript{6} and Hymenoptera sting.\textsuperscript{7}

In the latter, lesions consist of hives; a primary condition is necessary for it to develop and evolution is transient (symptoms triggered by the vibratory stimulus last until the primary condition is resolved).

On the basis of these observations, we believe that vibration can induce a heterogeneous set of diseases defined as vibratory urticaria or angioedema and propose a modification on the Kulthanan classification to incorporate some data included in the clinical descriptions of the cases (Table I).

In addition, Kulthanan et al\textsuperscript{1} included the 12 volunteers working in 2 dermatology departments in Spain that we reported\textsuperscript{8} as well as the population of 7 Chinese and 18 German medical students studied by Zhao et al.\textsuperscript{9} These individuals had a previous history of symptoms on vibratory stimuli according to questionnaires and usually different degrees of alteration of the vortex provocation test. To the best of our knowledge, none suffered...
from quality-of-life impairment, had ever consulted a physician, or required any treatments. In our opinion, further studies are needed to determine whether these 35 individuals truly correspond to pathological cases of acquired vibratory angioedema or rather exacerbated physiological responses to vibratory stimuli.

We agree with our colleagues that vibratory urticaria/angioedema should be correctly diagnosed, and we encourage others to share their experience in the published literature.

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Reply to “Proposal of a new classification of vibratory urticaria/angioedema”

To The Editor:

We thank Dr. Pastor-Nieto for her interest in our recent publication of a systematic review of vibratory angioedema (VA) and proposal for its classification.1,2 In line with Dr. Pastor-Nieto’s suggestion to subclassify hereditary VA (HVA), we distinguish 2 HVA subgroups, that is, due to a mutation in adhesion G protein-coupled receptor E2 (ADGRE2; 24 cases) and due to unknown cause (4 cases not investigated for their underlying genetic mutation).3,4 ADGRE2-mediated HVA manifests with transient whealing (<1 hour),5,4 whereas HVA patients with unknown mutation have angioedema (hours to days). This may suggest that HVA in the latter patients is not due to ADGRE2, but does not exclude this. Further analyses of these and other HVA patients are needed to understand if the described ADGRE2 mutation is the only mutation that drives HVA. Until further information becomes available, we prefer to subclassify HVA as “due to ADGRE2 mutation” and “due to unknown cause.”

Acquired vibratory angioedema (AVA) can present with wheals, angioedema, or both, and disease activity ranges from mild to severe.AVA may, therefore, be subclassified by clinical phenotypes or by disease activity. Dr. Pastor-Nieto’s suggestion to subclassify AVA as primary and secondary, that is, AVA without and with an underlying cause, respectively, is interesting. Two of 55 AVA patients (3.6%) had a potential cause, that is, a Candida glabrata urinary tract infection6 and a Hymenoptera sting.7,8 Secondary cases of cold urticaria, a form of chronic inducible urticaria (ClU) like AVA, have been described, anecdotally, but this is not very helpful.8 The pathogenesis and cause(s) of ClU...