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# Voice Biomarkers: The Most Modern and Least Invasive Tool for Coronary Assessment?

See also page 835

Currently, risk stratification for future cardiovascular events is based largely on the presence of traditional cardiovascular risk factors. However, the limited sensitivity and specificity of risk prediction algorithms incorporating these risk factors alone can result in misclassification and therefore overtreatment and undertreatment of those at greatest risk. Thus, much research effort has been invested in trying to identify various clinical features, or indeed biologic signatures (biomarkers), that can improve the discriminative capacity of these risk stratification tools. C-reactive protein<sup>1</sup> and computed tomography coronary calcium scoring<sup>2</sup> are two examples, both of which have been shown to improve mortality risk prediction above and beyond traditional risk factors. However, the requirement for blood sampling or, more importantly, ionizing radiation with these two biomarkers makes them imperfect for widespread use and could be a limiting factor in their translation to the clinical arena at large.

What is more, in the current COVID-19 climate, remote consultations and assessments are gaining an emerging importance to reduce face-to-face contact between patients, with other patients, and with clinical staff. This requirement for telemedicine is anticipated to continue long into the future and is developing at great pace, involving both start-up medical technology companies and mammoth established technology conglomerates alike (eg, Apple). To date, telemedicine approaches with wearable technologies have been used to record various biometric data, including cardiac rhythm, blood pressure, and oxygen saturations. Detection of these parameters with subsequent treatments (eg, anticoagulation

for subclinical atrial fibrillation<sup>3</sup>) has the capability to improve long-term morbidity and mortality, but this is yet to be proven. Indeed, whereas telemedicine has the potential to improve the cost-effectiveness of health care delivery, techniques often rely on the purchase of expensive devices, limiting their general use.

In this latest issue of *Mayo Clinic Proceedings*, Sara et al<sup>4</sup> present their work “Noninvasive Voice Biomarker Is Associated With Incident Coronary Artery Disease Events at Follow-up,” using a voice biomarker collected with a smartphone application. If the benefit of this approach is proven, clinical translatability is truly significant.

The authors collected voice recordings using the Vocalis Health smartphone application from 108 patients undergoing clinically indicated coronary angiography and followed them up for a median of 24 months. The voice biomarker was derived from each recording (three per patient), and the mean biomarker value was calculated. The primary end point was a composite of presenting to the hospital with chest pain or being diagnosed with an acute coronary syndrome (representing unstable disease); the secondary end point was a composite of a positive stress test result or the presence of coronary artery disease on coronary angiography at follow-up (representing stable disease). After adjustment for severity of coronary artery disease at baseline, higher mean voice biomarker levels strongly related to both the primary and secondary outcomes.

In earlier work from the group using similar voice signal characteristic analysis in the same population of patients, an analogous voice biomarker was defined from three recordings (reading a text, describing a positive emotional experience, describing a

negative emotional experience) in patients undergoing coronary angiography vs controls. The authors identified two vocal features that were independently associated with coronary artery disease.<sup>5</sup> By use of artificial intelligence techniques, a single voice biomarker has been subsequently identified and relationships established with heart failure admissions and mortality<sup>6</sup> as well as with elevated pulmonary artery pressures.<sup>7</sup> What the present study adds to these earlier works is crucial if the voice biomarker is to enter the clinical arena: the ability to predict clinical events. It is this powerful information that can enable individualized risk prediction, highlighting patients for optimized medical therapy for those at greatest risk of future cardiovascular events. Although there were few confirmed acute coronary syndrome events in this study (four patients suffered from unstable angina, one non-ST-segment elevation myocardial infarction, and zero ST-segment elevation myocardial infarction), there was a strong relationship between the voice biomarker and presentation with chest pain as well as the development of significant coronary atherosclerosis.

It would be prudent to assess whether it is possible to modulate voice biomarker levels with therapeutic strategies to provide an idea as to whether this biomarker represents a therapeutic target. To this end, in a post hoc study, the authors analyzed a follow-up voice biomarker at six months from the baseline reading and examined for changes over time. No detectable differences were identified in those undergoing percutaneous coronary intervention or those who had changes in baseline to follow-up noninvasive stress testing or coronary angiography. Thus, in this study, the biomarker did not change significantly with relief of coronary stenosis or the development or relief of ischemia. Like with other biomarkers (eg, C-reactive protein representing inflammation and computed tomography calcium scoring representing calcific coronary atherosclerosis), it is important to establish the mechanism underlying these vocal biomarker levels. One suggested

pathobiologic link includes atherosclerosis affecting the blood vessels supplying the organs of phonation. It would be difficult to show in this population whether the voice biomarker levels directly relate to coronary atherosclerosis, particularly given the results of the follow-up study. Conversely, it is more conceivable that the voice biomarker represents a picture of systemic health or perhaps inflammation. Another important potential biologic explanation for the voice biomarker is stimulation of the vagus nerve, which is important in both voice production and heart rate regulation. Accordingly, up-regulation of the autonomic nervous system due to chest pain or ischemia may be apparent in the voice analysis by neural mediation, before occurrence of a more clinically significant event.

Further work will be needed, in larger and more diverse cohorts in different languages, at baseline with long-term follow-up, before clinical utility for the risk stratification of cardiovascular events can be rolled out internationally. However, this study provides a vital and seminal first step on the path to establishing clinical usefulness by predicting future chest pain occurrences that result in hospital admission/acute coronary syndromes or progression of coronary atherosclerosis. If this work can be successfully translated, the far-reaching potential in cardiovascular disease is massive, crucially underpinned by its reliance on a smartphone application only.

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